LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

1600 STEWART AVENUE, WESTBURY, NY 11590
(516) 222-6222 • FAX (516) 683-1887

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OVERNIGHT COURIER 2/12/04

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug products, Fentanyl Transdermal System, in strengths of 37.5 mcg/hr, 62.5 mcg/hr and 87.5 mcg/hr are suitable for consideration in an abbreviated new drug application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that Fentanyl Transdermal Systems, in strengths of 37.5 mcg/hr, 62.5 mcg/hr, and 87.5 mcg/hr are suitable for submission in an ANDA. The designated reference-listed drug product upon which this petition is based is Duragesic® (Fentanyl Transdermal System) 25 mcg/hr. The Duragesic® product is also approved in strengths of 50 mcg/hr, 75 mcg/hr and 100 mcg/hr. All of the Duragesic® products are manufactured by Alza Corporation (see listing of the Duragesic® Application Number NDA 19-813 on page 3-158 of the 23rd Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) (Attachment 1)). Therefore, the petitioner seeks a change in strength (from the approved 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr product strengths to include intermediate strengths of 37.5 mcg/hr, 62.5 mcg/hr, and 87.5 mcg/hr Transdermal Systems) from that of the listed drug product for use in providing the ability to titrate a patient to a required dose between two currently approved doses.

B. Statement of Grounds

The reference-listed drug (RLD) product is currently available in strengths of 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr of Fentanyl. The proposed drug product represents a transdermal system that contains strengths that represent intermediate strengths exactly mid-way between those of the approved reference-listed drug products. None of the proposed strengths are lower than the lowest approved strength nor are any of the strengths greater than the highest approved strength. Inclusion of the intermediate strengths of the proposed drug product (37.5 mcg/hr, 62.5 mcg/hr, and 87.5 mcg/hr) will provide a dose mid-way between the

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currently approved and available strengths. These additional proposed strengths are consistent with the currently approved RLD product's labeling. Duragesic's® approved labeling indicates that the product should be titrated to control pain and that "each patient should be maintained at the lowest dose providing acceptable pain control". The availability of a 37.5 mcg/hr, 62.5 mcg/hr, and 87.5 mcg/hr product will provide greater flexibility in regard to selecting an appropriate specific intermediate dose that will provide the needed pain relief as determined by the prescribing physician and dictated by individual patient's condition and response. The petition is thus seeking a change in strength (from the existing 25 mcg/hr reference-listed drug, and the other approved strengths [50 mcg/hr, 75 mcg/hr, and 100 mcg/hr] transdermal systems to include a 37.5 mcg/hr, 62.5 mcg/hr, and 87.5 mcg/hr product) from that of the reference-listed drug.

The approved labeling of the RLD provided suggests that the dose of Fentanyl must be carefully individualized for each patient due to the potential for serious or life-threatening hypoventilation. This potent narcotic agent is indicated for treatment of chronic pain (such as that of malignancy) that:

- **Cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids; and**
- **Requires continuous opioid administration.**

Contraindications for starting doses exceeding 25 mcg/hr at the initiation of opioid therapy are also outlined in a Black Box Warning. Therefore, for non-opioid tolerant patients, starting doses above 25 mcg/hr are clearly not appropriate.

In addition, the labeling clearly states that

> **In patients with chronic pain, it is possible to individually titrate the dose of the transdermal system to minimize the risk of adverse effects while providing analgesia.**

The usually initial dosage for non-opioid tolerant patients is **not to exceed** 25 mcg/hr. For initial dose selection for opioid tolerant patients, the labeling of the reference-listed drug product provides a conversion table based on the equianalgesic potency of various oral or parenteral opioid products. The physician is provided a table that relates the current daily oral morphine equivalent dose to a recommended initial Duragesic® dose. This chart can be found in the labeling of the reference-listed drug product.

The above-referenced conversion chart lists Fentanyl dosage recommendations based on a total daily Morphine equivalent dose. The dose equivalents suggested for Fentanyl dose selection represent a fairly wide range of Morphine equivalent doses that are equated to each currently available strength of Fentanyl Transdermal Systems. In addition, the labeling of the reference-listed drug product cautions that the recommended starting dose may be too low for 50% of the patients. The availability of a 37.5 mcg/hr, 62.5 mcg/hr, and 87.5 mcg/hr transdermal system will offer an alternative intermediate dosage based on patient response by adding dosage strengths that are exactly mid-way between the existing currently approved strengths.

Likewise, because of the potentially fatal side effects of Fentanyl, extreme care must be taken in titrating a patient to an effective tolerable dose. Dosing instructions in the RLD advise that doses must be individualized based upon the status of each patient and should be assessed at regular intervals after Fentanyl transdermal system application. The patient should be maintained at the lowest dose providing acceptable pain control. The inclusion of the proposed intermediate strength products would allow the physician additional flexibility in providing appropriate intermediate doses not available by use of the currently approved strengths for certain patients. For instance, in a case where a patient's pain is not adequately controlled on a 25 mcg/hr patch, the physician's only current option would be to increase the patient's dose two fold to a 50 mcg/hr patch or add supplemental opioid therapy. However, if the 50 mcg/hr system produces undesirable side effects or the addition of supplemental oral opioid therapy is precluded by intolerance due to severe nausea or vomiting or dysphasia, the availability to reach an intermediate dose by adding the availability of a 37.5 mcg/hr strength transdermal patch to the choices available to the physician would provide a dose between the 25 mcg/hr and 50 mcg/hr dose and may provide the necessary increase in pain control while avoiding any undesirable side effects. This would, of course, be true for similar instances where the other intermediate proposed strengths could be considered when there may be a need to titrate between any of the other higher approved strength fentanyl transdermal system products.

The application of multiple systems (patches) to achieve the desired dose is also contemplated in the RLD product's labeling. The labeling of the RLD indicates that multiple systems may be applied for doses in excess of 100 mcg/hr. This would certainly imply that it would also be appropriate to utilize a second system to titrate a patient to an intermediate dose above the available 100 mcg/hr strength patches. The availability of a 37.5 mcg/hr, 62.5 mcg/hr, and 87.5 mcg/hr would also aid in titration for doses above 100 mcg/hr by providing additional options for dosage selection by the physician.

Copies of labeling of the reference-listed drug product upon which this petition is based and proposed draft labeling for the proposed product are included in Attachments 2 and 3, respectively. The proposed labeling is the "same as" that of the RLD labeling with the exception of changes allowed because the manufacturer of the generic product differs. The Description and How Supplied section will list the additional proposed strengths of 37.5 mcg/hr, 62.5 mcg/hr, and 87.5 mcg/hr, as well as instructions for the use of these new systems to achieve an intermediate dose. These changes are clearly authorized by the regulations that permit differences in labeling based on an approved petition under 21 CFR 314.98. There are, however, no changes in the indications, uses or warnings from that of the reference-listed drug product.

Therefore, the petitioner requests that the Commissioner find that a change in strength from 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr transdermal systems of Fentanyl to include new strengths of 37.5 mcg/hr, 62.5 mcg/hr, and 87.5 mcg/hr to achieve intermediate doses mid-way between two currently approved doses for this product raises no questions of safety or effectiveness, and the Agency should, therefore, approve the petition.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the Agency.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Robert Pollock pk

Robert W. Pollock
Vice President
Lachman Consultant Services, Inc.
1600 Stewart Avenue
Westbury, New York 11590

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Attachments:
1. Page 3-158 of the 23rd Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations
2. Labeling of the Reference-Listed Drug Product
3. Proposed Draft Labeling for the Proposed Product

cc: Emily Thomas (OGD)

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